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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/902,615 | 07/10/2001 | Avi Ashkenazi | 10466/65 | 9850 |

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| EXAMINER | |
|---|---|
| SPECTOR, LORRAINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | |

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/902,615 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Lorraine Spector, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-41 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/5/2004 has been entered.

Claims 39-41 and 43 are pending and under consideration.

All rejections under 35 U.S.C. §112, second paragraph and the double patenting rejection are withdrawn in view of applicants amendments to the claims, and terminal disclaimer.

### *Claim Rejections - 35 USC § 101 and §112*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-41 and 43 remain rejected under 35 U.S.C. 101 for reasons cited in the Office Action mailed 4/23/2003. Applicants traversal of this rejection has been fully considered but is not deemed persuasive for reasons as follow:

Applicant argues that the inflammation observed in the skin vascular permeability assay, assay #64, was not due to an irritant or allergic response because the PRO1063 molecule was injected into a non-presensitized animal. This has been fully considered but is not found to be persuasive. If any type of irritant (including lye or acid) is injected under the skin of a non-presensitized animal, a positive result would be observed in Assay # 64. Thus, a positive result in the assay does not provide the skilled artisan with any information other than that the injected substance was an irritant.

Applicant refers to the declaration of Dr. Fong, submitted with the response under 37 CFR § 1.132. In the declaration, items 1-9, Dr. Fong states that Assay # 64 is known as the Miles assay and is well known in the art as an assay to identify proinflammatory molecules. Declarant states that proinflammatory molecules can directly or indirectly cause vascular

permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. Declarant states that these proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. Declarant states that these cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. Declarant states that these processes are critical and tightly regulated via diapedesis and extravasation steps. Declarant concludes that proinflammatory molecules are useful in treating infections, as local administration of the proinflammatory polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing infection at a faster rate. Declarant points to MCP-1 and MCP-2 as being useful to cause neutrophils to extravasate, other CXC chemokines as being useful to activate neutrophils, and other CXC chemokines as being useful to cause chemotaxis of T lymphocytes. Declarant states that inhibitors of proinflammatory molecules are useful to treat diseases characterized by abnormal immune cell response. Declarant states that proinflammatory molecules with angiostatic properties are useful in treating tumors. Declarant states that the Miles assay was initially developed when researching the effect of histamine on the vascular system. Declarant states that subsequent workers have developed the assay into a quantitative one. This has been fully considered but is not found to be sufficient to overcome the rejection. The Miles assay is useful as a preliminary screen for potential proinflammatory molecules. Basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be useful as a proinflammatory. For example, MCP-1 and MCP-2 are not only positive in the Miles assay, they were also shown to have the specific activity of causing the extravasation of neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of activating neutrophils or being chemotactic for T lymphocytes. As was discussed in the previous Office Action, the state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a proinflammatory molecule with specific activities, as opposed to a basic irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of

such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989) is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation.

In point 10, Declarant states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). Declarant refers to Hirahara et al. (1993, Thrombosis Res. 71:139-148) as showing that FXIII stabilized microvasculature, leading to less permeability, and therefore may be useful in treatment of SHP. This has been fully considered but is not found to be sufficient to overcome the rejection. In the instant case, the claimed PRO protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable.

In point 11, Declarant states that the Miles assay was used by Senger et al. (1983, Science 219:983-985) to show that a secreted factor called VPF caused vascular permeability. This has been fully considered but is not found to be sufficient to overcome the rejection. Senger et al. set out to determine why vessels lining the peritoneal cavities of rodents with ascites tumors display markedly greater permeability than vessels in control animals. Senger et al. only conclude that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger et al. do not suggest that VPR can be considered a pro-inflammatory molecule useful for treatment of injury or infection.

In point 12, Declarant states that Yeo et al. (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results. Declarant states that VPF (VEGF) tested positive in the skin vascular permeability assay and then anti-VPF antibodies were used to quantify the amount of VPF in the DELFIA. Declarant states that the DELFIA assay has greater

sensitivity. This has been fully considered but is not found to be sufficient to overcome the rejection. Yeo et al. do not assert that the DEFLIA assay or the Miles assay can be used to identify proinflammatory molecules that can be used to treat injury or infection. Yeo et al. disclose that VPF may be the same protein as VEGF, which has been shown to be a mitogen specific for endothelial cells, and may promote tumor angiogenesis via its mitogenic activity for endothelial cells. However, the specific and useful activity of VEGF as an angiogenic factor was not identified by the Miles assay or the DEFLIA assay. Significant further research had to be conducted to identify this specific and substantial activity.

In point 13, Declarant reviews the skin vascular permeability assay and refers to Exhibit I as showing a positive reaction for a PRO polypeptide. This has been fully considered but is not found to be sufficient to overcome the rejection. It is not clear that the PRO polypeptide shown in the exhibit is the same PRO polypeptide of the instant claims. Furthermore, the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the claimed PRO polypeptide without resorting to undue experimentation.

In point 14, Declarant provides his expert opinion that the PRO polypeptide that shows activity in the skin permeability assay has specific, substantial and credible utilities. Declarant states that the application discloses that the results of the skin permeability assay were further analyzed by histopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation. Declarant concludes that the vascular permeability observed was not due to histamine release or endothelial cell damage. Declarant asserts that the PRO polypeptides testing positive in the assay are useful to enhance immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases. Declarant further states that angiogenic or angiostatic properties of proinflammatory would find utility in controlling tumorigensis. This has been fully considered but is not found to be sufficient to overcome the rejection. The specification describes analysis of the results of the skin vascular permeability assay as follows:

> The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a

> minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

As this quotation shows, the Declarant is not entirely correct with respect to the facts. The PRO polypeptides used in the assay are not further analyzed by histopathological examination **to rule out inflammation due to endothelial cell damage or mast cell degranulation**. In this specific case, human PRO326 was found to be an irritant to guinea pigs. Such *might* indicate that PRO326 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO326, e.g. that the human PRO326 protein has an epitope that the guinea pigs were pre-sensitized to. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO326. Accordingly, the only inflammation that could be treated using anti-PRO326 agents at the time the invention was made is that actually caused by PRO326, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess PRO326 based upon the results in the specification as originally filed). It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides. Finally, Declarant's comments regarding angiogenic or angiostatic activities of the PRO polypeptides is off-point, since these activities were not disclosed in the specification. Finally, it is noted that opinion declarations are evaluated for the reasonableness and validity of the opinion; however, no weight is given to an opinion on the ultimate legal conclusion in issue.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-41 and 43 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. This rejection is maintained for reasons cited above with respect to the rejection under 35 U.S.C. §101.

***Rejections Over Prior Art***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39-41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Wu et al., U.S. Patent Number 6,046,030.

U.S. Patent Number 6,046,030 teaches a protein of SEQ ID NO: 5, having 50% identity to residues 1-1083 of SEQ ID NO: 294, and SEQ ID NO: 2, having 49.8% identity to residues 32-1036 of SEQ ID NO: 294. 21 lines 59 to column 22 line 17. Labeled antibodies are disclosed at column 23, lines 42-53. Because of the relatedness of Wu's sequences to those of SEQ ID NO: 294, Wu's antibodies would reasonably be expected to meet the limitations of the rejected claims. Applicants argument that the antibodies of Wu would not be considered to specifically bind to the protein of SEQ ID NO: 294 has been fully considered but is not deemed

persuasive. As used in the art, 'specific' is not necessarily synonymous with 'binds exclusively to' as urged by applicants. Rather, specificity is relative, such that antibodies 'specific' for one protein can bind to another protein with similar sequence. For example, antibodies specific to PDGF have, indeed, been described as binding to CTGF, as evidenced by U.S. Patent Number 5,783,187. Accordingly, antibodies to Wu's protein that also bind to the same epitopic structure of SEQ ID NO: 294 would be considered to be "specific", and the antibodies of Wu anticipate the claims.

Claims 39-41 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang et al., U.S. Patent Number 6,426,072.

U.S. Patent Number 6,426,072 teaches SEQ ID NO: 4, which has 74.8% identity to residues 608-737 of SEQ ID NO: 294.

Antibodies to the proteins, including single chain and humanized antibodies, are disclosed at column 50. Immunoassays using labeled antibodies are disclosed at col. 25. Because of the relatedness of Wang's sequences to those of SEQ ID NO: 294, Wang's antibodies would reasonably be expected to meet the limitations of the rejected claims. Applicants argument that Wang is not applicable as prior art is deemed not persuasive for reasons of record regarding the priority date of this application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A search of the protein sequence databases revealed the following prior art:

| Locus | Date | Author | Identity to SEQ ID NO:294 |
|---|---|---|---|
| Q9D332 | 6/1/01 | J. Kawai et al. | 86% to residues 378-1119 |
| O94898 | 5/1/99 | T. Nagase et al. | 58.4% to residues 47-1036 |
| P70193 | 2/1/97 | Y. Suzuki et al. | 50% to residues 1-1083 |

Claims 39-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. or Nagase et al. or Suzuki et al., any of the three in view of in view of Sibson et al., WO94/01548, for reasons of record in the previous Office Action. Applicants traversal that the term "specifically" excludes antibodies according to this rejection has been fully considered but is not deemed persuasive for reasons cited above.

***Conclusion***

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

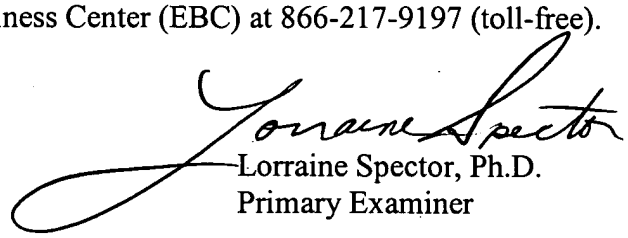
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner

2/3/05